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10/598,533	09/01/2006	Yoshinobu Yamazaki	Q96716	6983

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EXAMINER	
BLAKELY III, NELSON CLARENCE	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
07/09/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/598,533	YAMAZAKI ET AL.	
	Examiner	Art Unit	
	NELSON C. BLAKELY III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04/12/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *4,5 and 7-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/12/2007, 01/13/2009 and 02/26/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 1-12 of the instant application are pending. Claims 4, 5 and 7-12 are withdrawn pursuant to Applicant's Response, filed 04/12/2010. Accordingly, instant claims 1-3 and 6 are presented for examination on their merits.

Election/Restrictions

Applicant's elections ***without traverse*** of:

a) a disclosed indoline derivative represented by formula (I) as (-)-1-(3-hydroxypropyl)-5-((2R)-2-{[2-[(2,2,2-trifluoro-ethyl)oxy]phenyl}oxy)ethyl]amino}propyl)-2,3-dihydro-1H-indol-7-carboxamide (also known as KMD-3213 or silodosin);

b) at least one disclosed neurogenic disorder as spinal cord involvement; and

c) wherein the method does NOT further comprise administration in combination with one or more other agents, in the Reply filed on 04/12/2010,

are acknowledged.

Claims 4, 5 and 7-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected subject matter, there being no allowable generic or linking claim. Elections were made ***without traverse*** in the Reply filed on 04/12/2010.

Priority

Receipt is acknowledged of the certified copy, JP 2004-061476, filed 03/05/2004, submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. It is further acknowledged wherein said copy is not in English.

Information Disclosure Statement

The Information Disclosure Statements, filed 03/12/2007, 01/13/2009 and 02/26/2009, are acknowledged and considered.

The Information Disclosure Statement, filed 03/12/2007, fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. The NPL references, Teruhisa Ohashi and Osamu Ishizuka, do not disclose, at least, wherein the abstract is in English. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this Information Disclosure Statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Additionally, typographical corrections have been made to U.S. Patent Application Publication No. 2002/143007 (a "0" was inserted to read "2002/0143007") and NPL reference from Folia Pharmacologica Japonica (wherein the author, M. Yoshida *et al.* was added).

Applicant's Amendment

Applicant's Preliminary Amendment, filed 09/01/2006, wherein claims 1-5 are amended, and claims 6-12 are added, is acknowledged.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to use of legal phraseology, "comprise" (line 4).

Correction is required. See MPEP § 608.01(b).

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of overactive bladder accompanied with neurogenic disorders, does not reasonably provide enablement for prevention of overactive bladder accompanied with neurogenic disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As stated in the MPEP § 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. The nature of the invention
2. The state of the prior art
3. The predictability or lack thereof in the art
4. The amount of direction or guidance present
5. The presence or absence of working examples
6. The breadth of the claims
7. The quantity of experimentation needed, and
8. The level of skill in the art

It is noted that all of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The State of the Prior Art and the Predictability or lack thereof in the art

It is noted that Applicant provides wherein the present invention relates to pharmaceutical compositions which are useful for the prevention or treatment of overactive bladder accompanied with neurogenic disorders, in paragraph [0001], on page 1 of the instant specification. However, the generally accepted definition of "prevent" is to keep from occurring, or to anticipate. Therefore, by the Examiner's broadest reasonable interpretation of the claims to Applicant's method for preventing an overactive bladder accompanied with neurogenic disorders, the "prevention" of said disease lacks enablement due to an undue amount of experimentation required to predictably practice the prevention embodiments by Applicant's instant disclosure. Additionally, the art fails to provide compensatory guidance in the prevention of the onset of an overactive bladder. The Merck Manual reference (retrieved on 2010-07-04 from the Internet: <URL: http://www.merck.com/mmhe/sec11/ch147/ch147a.html?qt=urinary%20incontinence&alt=sh) discloses in the first two paragraphs under the *Introduction*, wherein urinary incontinence is the uncontrollable loss of urine, and may be caused by a bladder infection, certain drugs, brain and spinal cord disorders and diseases that affect the nerves leading to and from the bladder, for example. In the instant excerpt, The Merck Manual reference further discloses wherein the symptoms depend on the type of incontinence but may include a sudden uncontrollable urge to urinate or a constant leak

of urine. See page 2, lines 11-13 of the instant specification, wherein Applicant defines overactive bladder (OAB) as a disease based on symptoms of urgency, usually with frequency and with or without urge incontinence. Under the section entitled *Urge Incontinence*, bridging pages 3 and 4 of the document, The Merck Manual reference discloses wherein urge incontinence is an abrupt and intense urge to urinate that is followed by an uncontrollable loss of urine, and wherein urge incontinence is the most common type of established incontinence in older people, and often has no clear cause. Thus, since neither the instant specification, nor the prior or current art provides sufficient guidance as to how the method could be used to prevent an overactive bladder, it would require undue experimentation to practice the invention as broadly claimed.

The Amount of Direction or Guidance Present and Presence or Absence of Working Examples

The only direction or guidance present in the instant specification is in Example 1, page 14, wherein the compounds of the "general formula (I) exert an excellent improving effect on the frequency of the involuntary contraction and micturition interval as the parameter of urgency and frequency, respectively, in spinal cord injured OAB model, extremely useful for the prevention or treatment of OAB associated with neurogenic disorders". However, there are no data present in the specification for the "prevention" of said disease. The example only discloses wherein the compounds of the general formula (I) may be used to treat a spinal cord OAB model. It is not

discussed that said method can prevent the overactive bladder accompanied with neurogenic disorders.

The Breadth of the Claims

The instant breadth of the rejected claims is broader than the disclosure; specifically, the instant claims include "prevention" of *any* overactive bladder accompanied with neurogenic disorders.

The Quantity of Experimentation Needed and the Level of Skill in the Art

While the level of skill in the pharmaceutical arts is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prevent *any* overactive bladder accompanied with neurogenic disorders. The science of drug development has evolved such that, without guidance or working examples in the specification, the claims lack enablement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimoyama *et al.* (European Patent Application No. EP1358889A1; cited by Applicant), in view of Garvey *et al.* (U.S. Patent Application Publication No. 2002/0143007A1; cited by Applicant).

With regard to instant claims 1-3 and 6, Shimoyama *et al.* disclose, in reference claim 4, page 10, a method for the therapy of lower urinary tract symptoms wherein said method includes administration of an α_1 receptor blocker to a patient. In paragraph **[0017]**, page 3, Shimoyama *et al.* disclose wherein the α_1 receptor blocker may be KMD-3213, or (-)-1-(3-hydroxypropyl)-5-((2R)-2-{[2-[(2,2,2-trifluoro-ethyl)oxy]phenyl}oxy)ethyl]amino}propyl)-2,3-dihydro-1H-indol-7-carboxamide. Further, in paragraph **[0018]**, page 3, Shimoyama *et al.* disclose wherein KMD-3213 is a preferred drug of the invention. In paragraphs **[0002]** through **[0006]**, page 2,

Shimoyama *et al.* disclose wherein the bladder and urethra, which are called lower urinary tracts, participate in an urinary function which is controlled by three kinds of nerves, e.g., sympathetic nerve, parasympathetic nerve, and somatic nerve. In the instant excerpt, Shimoyama *et al.* further disclose wherein there are various causative diseases for the urinary disturbance, such as (1) organic obstruction of urethra, e.g., benign prostatic hyperplasia (or hypertrophy) and (2) abnormality of urination-controlling nerve (generally called neurogenic bladder), e.g., cerebrovascular accident, myelopathy (spina bifida, tethered cord syndrome), multiple sclerosis and spinocerebellar degeneracy. It is acknowledged, specifically in paragraphs **[0005]** and **[0007]**, page 2, wherein Shimoyama *et al.* disclose that tamsulosin (or Flomax®) has been used in the aforementioned causative diseases (1) and (2). Shimoyama *et al.* further disclose, in paragraph **[0008]**, page 2, another urinary disturbance (3), e.g., unstable bladder, which does not correspond to any of the apparent organic disturbance and neurological abnormality in lower urinary tracts. Additionally, in paragraph **[0015]**, page 3, Shimoyama *et al.* define the term "lower urinary tract symptoms" as a symptom of urinary disturbance due to a functional obstruction of lower urinary tract of both males and females, and does not include that which is due to disturbance of nerve controlling the lower urinary tract and that which is due to an organic disturbance of the lower urinary tract. See causative diseases (1) and (2).

However, as mentioned *supra*, Shimoyama *et al.* disclose wherein tamsulosin (or Flomax®) has been used in the causative diseases (1) and (2). Additionally, Shimoyama *et al.* disclose the use of tamsulosin hydrochloride in, at least, Examples 1-

11, wherein the reference invention is directed to the aforementioned causative disease (3). Therefore, a skilled artisan, at the time of the invention, would have construed embodiments wherein tamsulosin would have been effective in the therapy of lower urinary tract symptoms, as defined *supra*. Furthermore, one of ordinary skill would have construed an embodiment wherein KMD-3213, a preferred drug of the reference invention, as disclosed *supra*, would have also been effective in said method. "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)) and MPEP § 2123. Moreover, Garvey *et al.* disclose, in the Abstract, methods for treating benign prostatic hyperplasia (or hypertrophy), neurodegenerative disorders, urge incontinence or overactive bladder, wherein the α-adrenergic receptor antagonist is KMD-3213. See also reference claims 58 and 61.

Therefore, a skilled artisan would have envisaged the instantly claimed method for the treatment of overactive bladder accompanied with a spinal cord involvement, comprising the administration of KMD-3213, as disclosed by Shimoyama *et al.*, in view of Garvey *et al.* One of ordinary skill in the art would have been motivated to combine the teachings of the aforementioned references when seeking a method that effectively treats overactive bladder wherein a pharmacotherapy is preferred without the need of a risky and an invasive surgery. It would have been obvious to one of ordinary skill in the

art, at the time of the invention, because the combined teachings of the prior art are suggestive of the claimed invention.

Accordingly, the instant invention, as claimed in claims 1-3 and 6, is *prima facie* obvious over the combination of the aforementioned teachings.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NELSON C. BLAKELY III whose telephone number is (571) 270-3290. The examiner can normally be reached on Mon - Thurs, 7:00 am - 5:30 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614
July 5, 2010

/N. C. B. III/
Examiner, Art Unit 1614